PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

CLORAZEPATE

Clorazepate dipotassium

Capsules, 3.75 mg, 7.5 mg and 15 mg, oral

ATC Code: N05BA05

Anxiolytic-Sedative

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RECENT MAJOR LABEL CHANGES

1 Indications, 1.2 Geriatrics	12/2021
3 Serious Warnings and Precautions Box	12/2021
4 Dosage and Administration, 4.1 Dosing considerations	12/2021
7 Warnings and Precautions	12/2021
7 Warnings and Precautions, 7.1.4 Geriatrics	12/2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CLORAZEPATE (clorazepate dipotassium) is indicated for:

- the short-term symptomatic relief of excessive anxiety and tension in psychoneurotic patients including those with functional somatic complaints.
- the adjunctive management of acute alcohol withdrawal.

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 4.2 Recommended Dose and Dosage Adjustment; 7.1.4 Geriatrics.

Long-term use of CLORAZEPATE should be avoided in elderly patients. Enhanced monitoring is recommended. See 7 WARNINGS AND PRECAUTIONS,

Falls and **fractures**; 4.1 Dosing considerations.

2 CONTRAINDICATIONS

CLORAZEPATE is contraindicated in:

- Patients with known hypersensitivity to clorazepate dipotassium or to any non-medicinal ingredient in the formulation. For a complete listing, See 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with myasthenia gravis.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Addiction, Abuse and Misuse

The use of benzodiazepines, including CLORAZEPATE, can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing CLORAZEPATE
- Monitor all patients regularly for the development of these behaviours or conditions.
- CLORAZEPATE should be stored securely to avoid theft or misuse.

Withdrawal

Benzodiazepines, like CLORAZEPATE, can produce severe or life-threatening withdrawal symptoms.

- Avoid abrupt discontinuation or rapid dose reduction of CLORAZEPATE.
- Terminate treatment with CLORAZEPATE by gradually tapering the dosage schedule under close monitoring.

See 7 WARNINGS AND PRECAUTIONS,

Dependence**/Tolerance**.

Risks from Concomitant use with Opioids

Concomitant use of CLORAZEPATE and opioids may result in profound sedation, respiratory depression, coma and death. See 7 WARNINGS AND PRECAUTIONS, General

Concomitant use with opioids.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The dosage of CLORAZEPATE (clorazepate dipotassium) must be individualized and carefully titrated in order to avoid excessive sedation or mental and motor impairment.

As with other anxiolytic sedatives, short courses of treatment should usually be the rule for the symptomatic relief of disabling anxiety in psychoneurotic patients and the initial course of treatment should not last longer than 1 week without reassessment of the need for a limited extension. Initially, not more than 1 week's supply of the drug should be provided and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to short courses of therapy.

- CLORAZEPATE should always be prescribed at the lowest effective dose for the shortest duration possible.
- CLORAZEPATE can produce withdrawal signs and symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal
- ; 7 WARNINGS AND PRECAUTIONS,
- Dependence**/Tolerance**. Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.

- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Geriatric patients in particular may be more sensitive to benzodiazepines. See 7 WARNINGS AND PRECAUTIONS,
- Falls and **fractures**
- .
- Long-term use of CLORAZEPATE should be avoided in elderly patients. Enhanced monitoring is recommended.

4.2 Recommended Dose and Dosage Adjustment

Anxiety

CLORAZEPATE (clorazepate dipotassium) is administered orally in divided doses.

Usual adult daily dose: The usual adult daily dose is 30 mg. The dose should be adjusted gradually within the range of 15 to 60 mg in accordance with the response of the patient. After the patient has been stabilized on a suitable dosage, the frequency of dosing may be decreased in some patients to twice daily or once daily with the major portion of the dosage given at night, provided that the physician can ascertain that such a schedule will produce the desired anxiolytic effect without a period of drowsiness or impairment of mental functions.

Elderly or Debilitated Patients: In these patients, treatment should be initiated with 3.75 mg once a day, preferably at night. The dosage should be very carefully and gradually adjusted, depending on tolerance and response. See 7.1.4 Geriatrics.

Since anxiolytic sedatives are indicated for the treatment of current or state anxiety, administration of CLORAZEPATE should generally be limited to the duration of the episode requiring symptomatic relief.

Acute alcoholic withdrawal

For the management of acute alcoholic withdrawal, the following dosages may be used: 30-90 mg in divided doses in the first 24 hours, depending on individual tolerance and response. In the second 24 hours, the dosage should be reduced to not more than 60 mg in divided doses.

Subsequently, the daily dosage should be reduced gradually, usually to not more than 15-30 mg on the 4th day, and should then be tapered off more rapidly and discontinued as soon as possible.

Pediatrics (<18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. See 7.1.3 Pediatrics.

4.5 Missed Dose

If the patient misses a dose, inform the patient to skip the missed dose and take the next dose at the regular dosing schedule.

5 OVERDOSAGE

Symptoms

Clorazepate dipotassium overdosage may be manifested by varying degrees of CNS depression ranging from drowsiness, confusion, ataxia to coma. Hyporeflexia may occur. Unless the overdosage is extreme, effects on pulse, blood pressure and respiration are minimal.

Treatment

There are no specific antidotes for clorazepate. The treatment of overdosage should consist of the general measures employed in the management of overdosage of any CNS depressant.

If vomiting has not occurred spontaneously and the patient is fully awake, it may be induced with syrup of ipecac 20 to 30 mL.

Hypovolemia, indicated by reduced central venous pressure, should be treated, if present, with a balanced salt solution.

Although hypotension is rarely reported, it may occur with large overdoses and in this situation the use of pressor agents, such as levarterenol or metaraminol, should be considered.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule 3.75 mg, 7.5 mg and 15 mg of clorazepate dipotassium	Each capsule fill contains cornstarch, lactose monohydrate and stearic acid. The following are the capsule shell ingredients: black iron oxide, D&C red #33 and D&C yellow #10 (in 7.5 mg capsule only), gelatin, pharmaceutical ink and titanium dioxide.

Each CLORAZEPATE 3.75 mg capsule contains 3.75 mg of clorazepate dipotassium. Each 3.75 mg hard gelatin capsule consists of an iron gray opaque body and a white opaque cap, imprinted 3.75 in black pharmaceutical ink.

Each CLORAZEPATE 7.5 mg capsule contains 7.5 mg of clorazepate dipotassium. Each 7.5 mg hard gelatin capsule consists of an iron gray body and maroon opaque cap, imprinted 7.5 in black pharmaceutical ink.

Each CLORAZEPATE 15 mg capsule contains 15 mg of clorazepate dipotassium. Each 15 mg hard gelatin capsule consists of and iron gray opaque body and cap, imprinted 15 in black pharmaceutical ink.

CLORAZEPATE is supplied as capsules, in bottles of 100, 500 and 1000.

7 WARNINGS AND PRECAUTIONS

General

Concomitant use with opioids: Concomitant use of benzodiazepines, including CLORAZEPATE, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; 9.1 Serious Drug Interactions.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with benzodiazepines.

If a decision is made to prescribe CLORAZEPATE concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of CLORAZEPATE than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking CLORAZEPATE, prescribe a lower initial dose of the opioid analgesic and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. See 5 OVERDOSAGE**.**

Advise both patients and caregivers about the risks of respiratory depression and sedation when CLORAZEPATE is used with opioids.

Advise patients not to drive or operate heavy machinery with concomitant use of the opioid.

Dependence/Tolerance

Use of benzodiazepines, such as CLORAZEPATE, can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol, or illicit drugs.

The risk of dependence increases with higher doses and longer term use but can occur with short-term use at recommended therapeutic doses. The risk of dependence is greater in patients with a history of psychiatric disorders and/or substance (including alcohol) use disorder.

- Discuss the risks of treatment with CLORAZEPATE with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing CLORAZEPATE. In individuals prone to

substance use disorder, CLORAZEPATE should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- CLORAZEPATE should always be prescribed at the lowest effective dose for the shortest duration possible.
- All patients receiving benzodiazepines should be routinely monitored for signs and symptoms of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

Withdrawal: Benzodiazepines, such as CLORAZEPATE, can produce withdrawal signs and symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk of withdrawal is higher with higher dosages and/or prolonged use, but can occur with short-term use at recommended therapeutic doses.

The onset of withdrawal signs and symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may be difficult to distinguish from a relapse of the patient's condition.

Severe or life-threatening signs and symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behaviour.

Other withdrawal signs and symptoms include abdominal cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and physical contact, insomnia, irritability, muscle ness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their healthcare professional in order to discontinue safely.
- Patients experiencing withdrawal symptoms should seek immediate medical attention.

See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, Withdrawal

; 4.1 Dosing Considerations.

Driving and Operating Machinery

Patients on clorazepate dipotassium should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating dangerous machinery, including motor vehicles.

Falls and fractures

There have been reports of falls and fractures among benzodiazepine users due to adverse reactions

such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly or debilitated patients.

Hematology
Patients on CLORAZEPATE for prolonged periods should have blood counts and liver function tests periodically.

Hepatic
Patients on CLORAZEPATE for prolonged periods should have blood counts and liver function tests periodically. The usual precautions in treating patients with impaired hepatic function should also be observed.

Immune
Severe Anaphylactic and Anaphylactoid Reactions: Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including CLORAZEPATE. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with CLORAZEPATE should not be rechallenged with the drug.

Monitoring and Laboratory Tests
Patients on CLORAZEPATE for prolonged periods should have blood counts and liver function tests periodically.

Neurologic
Since clorazepate dipotassium has a central nervous system depressant effect, patients should be advised against the simultaneous use of other CNS depressant drugs and cautioned that the effects of alcohol may be increased.

Complex sleep-related behaviours: Complex sleep-related behaviours such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in patients who have taken **CLORAZEPATE.** Other potentially dangerous behaviours have been reported in patients who got out of bed after taking a sedative-hypnotic and were not fully awake, including preparing and eating food, making phone calls, leaving the house, etc. As with "sleep-driving", patients usually do not remember these events. The use of alcohol and other CNS-depressants with **CLORAZEPATE** appears to increase the risk of such behaviours, as does the use of **CLORAZEPATE** at doses exceeding the maximum recommended dose. **CLORAZEPATE** is not to be taken with alcohol. Caution is needed with concomitant use of other CNS depressant drugs. Due to the risk to the patient and the community, discontinuation of **CLORAZEPATE** should be strongly considered for patients who report any such complex sleep-related behaviours.

Memory disturbance: Anterograde amnesia of varying severity has been reported following therapeutic doses of benzodiazepines. The event is rare with CLORAZEPATE. Anterograde amnesia is a dose-related phenomenon and elderly subjects may be at particular risk.

Ophthalmologic

Narrow-angle Glaucoma: CLORAZEPATE should be given with caution, if at all, to patients with acute narrow-angle glaucoma.

Psychiatric

CLORAZEPATE (clorazepate dipotassium) is not recommended for use in depressive neuroses or in psychotic reactions.

Abnormal thinking and psychotic behavioural changes have been reported to occur in association with the use of benzodiazepines including CLORAZEPATE, although rarely. Some of the changes may be characterized by decreased inhibition, e.g., aggressiveness or extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (e.g., sedative/hypnotics). Particular caution is warranted in patients with a history of violent behaviour and a history of unusual reactions to sedatives including alcohol and the benzodiazepines. Psychotic behavioural changes that have been reported with benzodiazepines include bizarre behaviour, hallucinations, and depersonalization. Abnormal behaviours associated with the use of benzodiazepines have been reported more with chronic use and/or high doses but they may occur during the acute, maintenance or withdrawal phases of treatment.

It can rarely be determined with certainty whether a particular instance of abnormal behaviour listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric disorder. Nevertheless, the emergence of any new behavioural sign or symptom of concern requires careful and immediate evaluation.

Confusion: The benzodiazepines affect mental efficiency, e.g., concentration, attention and vigilance. The risk of confusion is in greater in the elderly and in patients with cerebral impairment.

Depression: Caution should be exercised if CLOREZEPATE is prescribed to patients with signs or symptoms of depression that could be intensified by hypnotic drugs. The potential for self-harm (e.g., intentional overdose) is high in patients with depression and thus, the least amount of drug that is feasible should be available to them at any one time.

Use in Mental and Emotional Disorders: Benzodiazepines, such as CLORAZEPATE, are not recommended in the treatment of psychotic or severely depressed patients. It should be recognized that suicidal tendencies may be present and that protective measures may be necessary. Since excitement and other paradoxical reactions may result from the use of the drug in psychotic patients, it should not be used in ambulatory patients suspected of having psychotic tendencies.

Renal

The usual precautions in treating patients with impaired renal function should also be observed.

Reproductive Health: Female and Male Potential

Teratogenic Risk: Several studies have suggested an increased risk of congenital malformations associated with the use of the benzodiazepines, chlordiazepoxide and diazepam, and meprobamate,

during the first trimester of pregnancy. Malformations in the infant of a mother who had taken clorazepate during the first trimester of pregnancy has been reported.

Nonteratogenic Risk: Nordiazepam, the active metabolite of clorazepate, crosses the human placenta. It is to be considered that the child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms from the drug, during the postnatal period. Also, neonatal flaccidity has been reported in an infant born of a mother who had been receiving benzodiazepines.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of use of clorazepate dipotassium in pregnancy has not been established. Therefore, CLORAZEPATE is not recommended for use during pregnancy. Nordiazepam, the active metabolite of clorazepate, crosses the human placenta. Several studies have suggested an increased risk of congenital malformations associated with the use of the benzodiazepines, chlordiazepoxide and diazepam, and meprobamate, during the first trimester of pregnancy. Malformations in the infant of a mother who had taken clorazepate during the first trimester of pregnancy has been reported. Since clorazepate dipotassium is also a benzodiazepine derivative, its administration is rarely justified in women of child-bearing potential. If the drug is prescribed to a woman of child-bearing potential, she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become or suspects that she is pregnant.

7.1.2 Breast-feeding

CLORAZEPATE is not recommended for use during breast-feeding since nordiazepam, the active metabolite of clorazepate is excreted in human breast milk.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to CNS depression after even low doses of benzodiazepines. Therefore, medication should be initiated in these patients with very low initial doses, and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation or neurological impairment.

Long-term use of CLORAZEPATE should be avoided in elderly or debilitated patients who may be more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The side effect most frequently reported is drowsiness. Less commonly reported (in descending order of occurrence) are: dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache and mental confusion. Other side effects include insomnia, transient skin rashes, fatigue, ataxia, genito-urinary complaints, irritability, diplopia, depression, slurred speech and hypotension.

There have been reports of abnormal liver and kidney function tests and of a decrease in hematocrit. Decrease in systolic blood pressure has been observed with clorazepate.

8.5 Post-Market Adverse Reactions

Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly and debilitated patients.

Dependence/Withdrawal: Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as CLORAZEPATE. Severe and life-threatening symptoms have been reported. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; 7 WARNINGS AND PRECAUTIONS,

Dependence**/Tolerance**.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Concomitant use of CLORAZEPATE and opioids may result in profound sedation, respiratory depression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

See 7 WARNINGS AND PRECAUTIONS, General

Concomitant use with opioids**General**

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9.4 Drug-Drug Interactions

Potentiation of Drug Effects

If CLORAZEPATE is to be combined with other drugs acting on the central nervous system, careful consideration should be given to the pharmacology of the agents to be employed. Animal experience indicates that clorazepate prolongs the sleeping time after hexobarbital or after ethyl alcohol, increases the inhibitory effects of chlorpromazine, but does not exhibit monoamine oxidase inhibition. Clinical studies have shown increased sedation with concurrent hypnotic medications. The action of the benzodiazepines may be potentiated by barbiturates, narcotics, phenothiazines, monoamine oxidase inhibitors, or other antidepressants.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

CLORAZEPATE (clorazepate dipotassium) possesses anxiolytic and sedative properties that have been found to be of value for the symptomatic relief of pathological anxiety and tension states in psychoneurotic patients.

Clorazepate produces electroencephalographic changes similar to those of some of the other benzodiazepines, with an increased average frequency, frequency deviation and fast beta activity, while alpha activity and amplitudes decrease. In electroencephalographic studies of sleep, clorazepate produced decreased deep sleep stages with REM activity attenuated, although not significantly.

10.2 Pharmacodynamics

Clorazepate dipotassium has central nervous system depressant properties with a somewhat flatter dose-response curve than the sedative-hypnotic drugs.

Studies in laboratory animals showed that clorazepate dipotassium produced, in varying doses, taming, disinhibitory, sedative, anti-convulsant, muscle-relaxant, ataxic and hypnotic effects.

As with the sedative hypnotic drugs, benzodiazepines at sedative doses reduce slightly behavioural arousal, increase responsiveness to environmental stimuli, suppress passive avoidance behaviour, and increase approach behaviour. At slightly higher doses, they appear to increase errors of commission in performing tasks, produce drowsiness and ataxia, and decrease muscle tone. At low doses, clorazepate dipotassium does not reduce significantly locomotor activity.

Clorazepate dipotassium suppresses pentylenetetrazol-induced convulsions, but is relatively ineffective against maximal electroshock convulsions.

Clorazepate dipotassium has shown little or no effect on the autonomic nervous system.

After treatment of rats for one week, there was no indication that clorazepate dipotassium enhanced the activity of liver microsomal enzymes. It, however, possesses dependence liability and may produce withdrawal symptoms, but has a wide margin of safety against poisoning.

In rats, conditioned avoidance response was inhibited at an oral dose of 10 mg/kg and sedation was induced at 32 mg/kg. In monkeys, aggressive behaviour was reduced at an oral dose of 0.25 mg/kg and sedation (ataxia) was induced at 7.5 mg/kg.

10.3 Pharmacokinetics

Absorption

Following ingestion, the drug is rapidly decarboxylated to form nordiazepam (N- desmethyldiazepam) which is absorbed rapidly and is the primary active metabolite.

Distribution:

Peak serum levels of nordiazepam appear in from 1 to 2 hours following a single dose and the serum half-life is about 48 hours. During multiple dosage with clorazepate steady-state plasma concentrations of nordiazepam are usually attained in 5 days to 2 weeks. The concurrent use of antacids with clorazepate may decrease the rate and extent of conversion of the drug to desmethyldiazepam resulting in a small reduction (12%) in drug bioavailability.

Metabolism:

Subsequent hydroxylation of nordiazepam in the liver leads to the formation of oxazepam and p-OH-nordiazepam, which are excreted in the urine in conjugated and unconjugated forms.

Elimination

In man, approximately 52% of the urine drug level is found to be conjugated oxazepam. In 2 volunteers given 15 mg of 14C- clorazepate, about 80% was recovered in the urine and faeces within 10 days. Excretion was primarily in the urine with about 1% excreted per day on day 10.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-25°C) in a tightly closed container.

Keep out of reach and sight of children.

CLORAZEPATE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

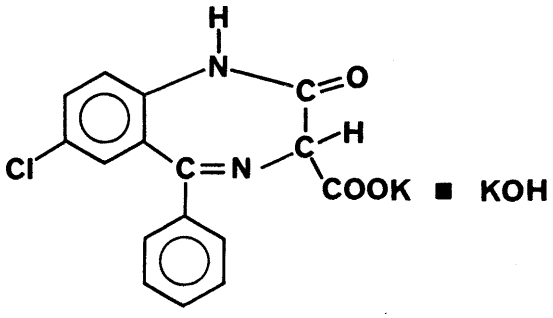
None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	clorazepate dipotassium
Chemical name:	dipotassium;7-chloro-2-oxo-5-phenyl-1,3-dihydro-1,4-benzodiazepine-3-carboxylate;hydroxide
Molecular formula and molecular mass:	$C_{16}H_{11}Cl\ K_2N_2O_4$ and 408.9
Structural formula:	Clorazepate dipotassium is a benzodiazepine and has the following structural formula:



14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity:

Animal Species	Sex	Oral LD_{50} (and 95% probability level inclusive of the 20% confidence limits) mg/kg
Mice*	F	2025 (1633-2511)

Animal Species	Sex	Oral LD_{50} (and 95% probability level inclusive of the 20% confidence limits) mg/kg	
	M	1850	(1394-2456)
	Combined	1915	(1655-2216)
Rats*	F	1360	(1048.9-1763.3)
	M	1650	(1427.7-1907.0)
	Combined	1440	(1299.7-1595.5)

* 9 groups, each with 5 animals/sex were treated with the test article (clorazepate dipotassium) at logarithmically spaced doses.

Mortality generally occurred over a 48 hour period post-dosing.

Signs of systemic toxicity were ptosis, reduced activity and ataxia, piloerection, dyspnea or bradypnea, epistaxis, lacrimation, perineal staining, hunchback and coma.

Necropsy of these animals generally revealed darkening of the liver, paleness of the kidney and/or spleen, distension and/or irritation/hemorrhage of the stomach and or small intestine, distention of the urinary bladder and pulmonary congestion. Animals killed routinely at the conclusion of the study generally revealed no abnormality.

Subacute Toxicity Studies

Rats: It has been reported that rats could tolerate 50 times the human dose of clorazepate dipotassium administered daily by intubation for 78 weeks except for sedation, muscle relaxation and drowsiness. At higher doses (100 to 150 times the human dose) these effects were more marked. Pituitary chromphobe adenomatous hyperplasia in 4 of 10 females was also observed at higher doses.

Dogs: A 22 month oral chronic toxicity study in 24 dogs involving doses up to 75 mg/kg/day indicated that dogs could tolerate about 20 times the human dose of clorazepate dipotassium except for sedation, weight gain and reversible liver function disturbance. Higher doses produced more severe sedation and liver function disturbance. Liver mass increase and hepatic canalicular bile stasis without evidence of obstruction were observed at necropsies.

Monkeys: Rhesus monkeys (18) given increasing oral doses (from 3 mg/kg to 36 mg/kg/day) of clorazepate dipotassium could tolerate 18 to 36 times the human dose daily for 52 weeks. No significant differences were found between treated and control groups. Although total leukocyte count remained within normal limits it tended to fall in female monkeys at the highest doses.

Examination of all organs revealed no alterations attributable to the drug. No alteration of liver function or structure was observed.

Carcinogenicity:

No long-term animal studies have been performed to evaluate carcinogenic potential.

Genotoxicity:

No long-term animal studies have been performed to evaluate mutagenic potential**.**

Reproductive and Developmental Toxicology:

Reproductive Studies: Fertility, reproduction and teratology studies in rats at doses up to 150 mg/kg/day and in rabbits at doses up to 15 mg/kg/day produced no abnormalities in the fetuses. An increased resorption was observed in the rabbits and retarded ossification in the fetuses of the treated higher dose dams. Clorazepate dipotassium did not alter the fertility indices or reproductive capacity of adult animals. The sedative effect of higher doses interfered with the care of the young by their mothers.

Special Toxicology:

Information is not available.

Juvenile Toxicity:

Information is not available.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

CLORAZEPATE

Clorazepate dipotassium Capsules

Read this carefully before you start taking **CLORAZEPATE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CLORAZEPATE**.

Serious Warnings and Precautions

Addiction, Abuse and Misuse: Even if you take **CLORAZEPATE** exactly as you were told to, you are at risk for abuse, misuse, addiction, physical dependence and withdrawal. Abuse and misuse can result in overdose or death, especially if you take **CLORAZEPATE** with:

- opioids
- alcohol or
- illicit drugs

Your doctor should:

- talk to you about the risks of treatment with **CLORAZEPATE** as well as other treatment (including non-drug) options
- assess your risk for these behaviours before prescribing **CLORAZEPATE**
- monitor you while you are taking **CLORAZEPATE** for the signs and symptoms of misuse and abuse. If you feel like you are craving **CLORAZEPATE**, or not using it as directed, talk to your doctor right away.

Store **CLORAZEPATE** in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking **CLORAZEPATE**, lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms. See Other warnings you should know about.

- Always contact your doctor before stopping, or lowering your dose of **CLORAZEPATE** or changing your medicine.

CLORAZEPATE with Opioids: Taking **CLORAZEPATE** with opioid medicines can cause:

- severe drowsiness
- decreased awareness
- breathing problems
- coma
- death

What is CLORAZEPATE used for?

- the short-term relief of severe anxiety and tension symptoms
- the management of alcohol withdrawal.

If you are 65 years or older, talk to your doctor before starting CLORAZEPATE. CLORAZEPATE may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

How does CLORAZEPATE work?

CLORAZEPATE belongs to the group of medicines called benzodiazepines. Benzodiazepines affect chemical activity in the brain to help with sleep and reduce anxiety and stress.

What are the ingredients in CLORAZEPATE?

Medicinal ingredients: Clorazepate dipotassium

Non-medicinal ingredients: capsule fill contains cornstarch, lactose monohydrate and stearic acid.

Capsule shell contains black iron oxide, D&C red #33 (7.5 mg capsule only), D&C yellow #10 (7.5 mg capsule only), gelatin, pharmaceutical ink and titanium dioxide.

CLORAZEPATE comes in the following dosage forms:

Capsule 3.75 mg, 7.5 mg and 15 mg

Do not use CLORAZEPATE if:

- you are allergic to clorazepate dipotassium or any other non-medicinal ingredients in this product.
- you have a long tern disease called myasthenia gravis. This causes weakness of muscles you use for movement.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CLORAZEPATE. Talk about any health conditions or problems you may have, including if you:

- have or had depression, mood problems or suicidal thoughts or behaviour
- have a history of abnormal thinking and behaviour (psychotic reactions)
- have impaired kidney or liver function
- have abused drugs in the past or find it difficult to stop taking medicines
- have eye problems or blurred vision
- are pregnant or planning to become pregnant
- are breastfeeding
- are elderly or weak, or have organic brain syndrome
- have lactose intolerance
- have ever had a problem with:

- substance use, including prescribed or illegal drugs, or
- alcohol

- have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)

Other warnings you should know about:

CLORAZEPATE may cause you to become drowsy or light-headed. Avoid driving, using heavy machinery or doing dangerous activities until you know how CLORAZEPATE affects you.

Do not drink alcohol or take drugs that make you sleepy while taking CLORAZEPATE without first talking to your healthcare professional.

Important:

1. Do not take more CLORAZEPATE than prescribed.
2. Do not take CLORAZEPATE when you drink alcohol.
3. Talk to your doctor about all your medicines, including over-the counter medicines and herbal products. You doctor will tell you if you can take CLORAZEPATE with your other medicine.
4. You and people close to you should watch unusual types of behavior when you are asleep. If you find out that you have done *any* such activities for which you have no memory, you should call your healthcare professional immediately.

Sleep-Related Behaviours:

Treatment with CLORAZEPATE can cause potentially dangerous sleeping-related behaviours such as getting out of bed while not fully awake and doing activities that you do not know you are doing. If this happens, you may not remember doing these activities when you wake up. This might happen when CLORAZEPATE is taken with alcohol or other drugs that can make you sleepy (e.g., medicines used to treat depression or anxiety). If you drink alcohol, do not take CLORAZEPATE. The activities you may do in these situations can put you and people around you in danger. This can include driving a car ("sleep-driving"), leaving the house, making and eating food, and talking on the phone.

Memory Problems:

In rare cases, CLORAZEPATE can cause a type of memory loss known as amnesia. This is shown by having difficulty remembering things that recently happened, usually several hours after taking the medication. If you are going to take CLORAZEPATE before sleeping, this is usually not a problem, but if you take CLORAZEPATE to help you sleep while travelling, such as during an airplane flight, you may wake up to memory lapse caused by the drug. This has been called "traveller's amnesia" and can be a problem. DO NOT TAKE CLORAZEPATE when a full night's sleep is not possible before you need to be active and functional (e.g., an overnight flight of less than 8 hours). Your body needs time to eliminate the medication.

Withdrawal: If you suddenly stop your treatment, lower your dose too fast, or switch to another medication, you can experience withdrawal symptoms that can range from mild symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop CLORAZEPATE.

Your risk of going through withdrawal is higher if you are taking CLORAZEPATE for a long time or at high

doses. However, symptoms can still occur if you are taking CLORAZEPATE as directed for a short period of time or slowly reducing the dose.

The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).

Tell your doctor right away if you experience any symptoms of withdrawal after changing or stopping your treatment.

Severe symptoms of withdrawal include:

- feeling like you cannot move or respond (catatonia)
- severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
- feeling depressed
- feeling disconnected from reality (dissociation)
- seeing or hearing things that are not there (hallucinations)
- overactive behavior and thoughts (mania)
- believing in things that are not true (psychosis)
- convulsions (seizures), including some that do not stop
- thoughts or actions of suicide

For other symptoms of withdrawal, see the Serious side effects and what to do about them table (below).

To reduce your chances of going through withdrawal:

- always contact your doctor before stopping or reducing your dose of CLORAZEPATE or changing medications
- always follow your doctor's instructions on how to reduce your dose carefully and safely
- tell your doctor right away if you experience any unusual symptoms after changing or stopping your treatment

CLORAZEPATE with Opioids: Taking CLORAZEPATE with opioid medicines can cause severe drowsiness and breathing problems.

Tell your doctor if you:

- are taking opioid medicines
- are prescribed an opioid medicine after you start taking CLORAZEPATE

Do NOT drive or operate heavy machinery or do tasks that require special attention if you are taking an opioid medicine and CLORAZEPATE.

Driving and using machines: CLORAZEPATE may affect your ability to be alert. This may be worse if you drink alcohol or take other sedatives. Do NOT drive or operate heavy machinery or do tasks that require special attention until you know how CLORAZEPATE affects you. Avoid driving or using machinery if taking CLORAZEPATE with other sedative.

Falls and Fractures: Benzodiazepines like CLORAZEPATE can cause you to feel sleepy, dizzy and affect your balance. This increases your risks of falling, which can cause fractures or other fall related-injuries, especially if you:

- take other sedatives
- consume alcohol
- are elderly or
- have a condition that causes weakness or frailty

Blood Tests: Monitoring and Tests:

Your healthcare professional may want to do blood tests if you are on certain medication to follow your progress. It is important that you do have your blood tested.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CLORAZEPATE:

- drugs to help you to sleep
- drugs to treat sleeplessness, convulsions or fits and headache (such as hexobarbital)
- drugs used to treat pain
- drugs used to treat mental and emotional disorders (such as chlorpromazine)
- Monoamine oxidase inhibitors, and other antidepressants used to treat depression
- Alcohol

Serious Drug Interactions

Taking CLORAZEPATE and opioids may cause:

- severe drowsiness
- trouble breathing
- coma
- death

How to take CLORAZEPATE:

Always take this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.

Take CLORAZEPATE capsules by mouth.

Usual dose:

CLORAZEPATE is not for use in children under 18 years of age.

For the management of anxiety:

Adults: The usual dose is 30 mg per day in divided doses. Your doctor may adjust the dose within the range of 15 to 60 mg depending on your condition.

Elderly and/or Debilitated Patients: Should start with 3.75 mg just before bedtime. Your doctor will adjust the dose carefully and gradually depending on your condition.

For the management of acute alcoholic withdrawal:

Your doctor will decide which dose you should take. Always follow your doctor's instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

Your doctor will slowly decrease your dose and will tell you when to stop taking the medicine. Always follow your doctor's instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

Overdose:

CLORAZEPATE overdosage include:

- drowsiness,
- confusion,
- difficulty with balance and walking, speaking and swallowing (ataxia),
- coma,
- Hyporeflexia (muscles are less responsive to stimuli) may occur.

If you think you, or a person you are caring for, have taken too much CLORAZEPATE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take CLORAZEPATE, do not take a double dose to make up for the forgotten dose. Take the next dose at the usual time.

What are possible side effects from using CLORAZEPATE?

These are not all the possible side effects you may have when taking CLORAZEPATE. If you experience any side effects not listed here, tell your healthcare professional.

Other side effects may include:

- trouble sleeping,
- skin rashes,
- feeling tired,
- impaired coordination,
- irritability,
- double vision,
- slurred speech,

- Falls and fractures

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
drowsiness	✓		
LESS COMMON			
dizziness, various gastrointestinal problems, nervousness, blurred vision, dry mouth, headache, confusion	✓		
RARE			
Amnesia (a type of memory loss): difficulty recalling events that recently happened		✓	
Mental and behavioral changes: Unexpected reactions such as agitation, anxiety, hyperactivity, excitement, hallucination, impaired concentration or memory, worsened insomnia, feeling nervous, irritable, increased muscle spasticity, aggressiveness, irritability, rages, psychoses and violent behavior		✓	
Severe allergic reaction: (swelling of the tongue or throat, trouble breathing, nausea and vomiting)			✓
Depression: Depressed mood; thoughts of death or suicide		✓	
VERY RARE			
Somnambulism: (sleepwalking) – getting out of bed while not fully awake and do activities you do not remember the day after		✓	
UNKNOWN FREQUENCY			
Overdose: extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure.			✓
Respiratory Depression: slow, shallow or weak breathing.			✓
Urinary problems	✓		

Serious side effects and what to do about them			
Symptoms / effects	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Withdrawal: **Severe symptoms include:** **Catatonia:** feeling like you cannot move or respond **Delirium Tremens:** severe confusion, shivering, irregular heartrate and excessive sweating **Feeling depressed** **Dissociation:** feeling disconnected from reality **Hallucinations:** seeing or hearing things that are not there **Mania:** overactive behaviour and thoughts **Psychosis:** believing in things that are not true **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **Thoughts or actions of suicide** **Other symptoms include:** Stomach cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a burning or prickling feeling in the hands, arms, legs or feet; sweating.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15-25°C) in a tightly closed container.

Keep out of reach and sight of children.

If you want more information about CLORAZEPATE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp; the manufacturer's website https://www.aapharma.ca/en/, or by calling 1-877-998-9097.

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